

Factors affects the implementation of active surveillance therapy for low-risk papillary thyroid microcarcinoma

Xueqi Zhang, Renaguli Aihaiti, Weiping Teng, Xiaoguang Shi

Department of Endocrinology and Metabolism, Institute of Endocrinology, National Health Commission (NHC) Key Laboratory of Diagnosis and Treatment of Thyroid Diseases, The First Hospital of China Medical University, Shenyang, Liaoning 110001, China.

To the Editor: Since the 1990s, the incidence of thyroid cancer (TC), especially papillary thyroid cancer (PTC), has increased significantly, while the mortality rate of PTC patients has been stable. Studies have confirmed that this phenomenon could be caused by overdiagnosis; Therefore, active surveillance (AS) therapy for low-risk papillary thyroid microcarcinoma (PTMC; T1aN0M0) must be promoted, and obstacles to its implementation must be addressed. In 2014, eight physicians from South Korea issued an open letter to the public to warn of the high incidence of TC and advise against the use of ultrasound; Subsequently, their views gained worldwide attention. In 2015, the American Thyroid Association (ATA) issued guidelines suggesting that fine-needle aspiration biopsy of thyroid nodules should be performed using a risk-stratified method, and nodules smaller than 1 cm without risk factors should generally not be biopsied.^[1] The guideline acknowledged for the first time that AS can be effective management for low-risk PTMC patients.

Chinese also exhibit the classic epidemiological features of TC overdiagnosis. The incidence rate of TC in China has sharply increased since 2000, while the mortality rate was very stable during the same period.^[2] However, under such severe conditions, few people have explored the clinical evidence for AS to provide an alternative therapy to surgery for low-risk PTMC patients. Despite the increasing recognition of AS, its application is still limited due to the unclear diagnosis of low-risk PTMC and insufficient supporting evidence on the benefits of AS. There are also other obstacles, such as the influence of family members, quality of life (QoL), and economic benefits. Analyzing the factors that promote and hinder the implementation of AS will contribute to its future development and application.

To date, credible supporting evidence has mainly come from a small number of countries. A Kuma Hospital study found that more than 70% of patients in the observation group had no change or showed a reduction in tumor size during follow-up, tumors expanded by more than 10 mm in 10.2% of patients, and lymph node metastasis (LNM) was present in only 1.2% of patients.^[3] Other studies from Japan had similar results, which recommended choosing AS to avoid surgical complications, even for multiple tumors. To confirm the role of AS, multiple multicenter prospective research protocols targeting low-risk PTMC patients have been registered. Italian scholars have pointed out that studies on Asian populations might not be suitable for European populations and it is vital to consider racial-specific differences when designing protocols. Thus, Chinese studies must draw on the experience of other countries and formulate management strategies based on our situation.

Even if AS has been implemented for low-risk PTMC patients, many of them still converted to surgery for reasons of the progression of diseases or psychological status, which are also among the important reasons why many doctors and patients are reluctant to apply AS. For example, a prospective study in Italy was initiated in 2014, which implied that only 3% of the patients had clinical progression and required surgery, and 20% had no disease progression but were switched to surgery. Despite delayed surgery, all of them had an excellent response.^[4] They, therefore, proposed that AS of low-risk PTMC patients is feasible and safe in the Italian medical context. Even if AS is not contraindicated, careful observation of tumor volume changes is required after implementation. Overall, a large proportion of the reasons for delayed surgery is not comprised of enlargement or LNM; Therefore, these conditions require optimal management.

Access this article online

Quick Response Code:


Website:
www.cmj.org

DOI:
10.1097/CM9.0000000000003083

Correspondence to: Xiaoguang Shi, Department of Endocrinology and Metabolism, Institute of Endocrinology, National Health Commission (NHC) Key Laboratory of Diagnosis and Treatment of Thyroid Diseases, The First Hospital of China Medical University, Shenyang, Liaoning 110001, China
E-Mail: xiaoguangshi_cmu@163.com

Copyright © 2024 The Chinese Medical Association, produced by Wolters Kluwer, Inc. under the CC-BY-NC-ND license. This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial-No Derivatives License 4.0 (CCBY-NC-ND), where it is permissible to download and share the work provided it is properly cited. The work cannot be changed in any way or used commercially without permission from the journal.

Chinese Medical Journal 2024;137(15)

Received: 22-02-2024; Online: 28-03-2024 Edited by: Jing Ni and Xuehong Zhang

There is a lack of agreement regarding accepted and reliable screening criteria, making doctors wary of using AS for patients. Brito *et al*^[5] proposed a risk-stratified framework to evaluate the suitability of PTMC patients for AS regimens requiring assessment of three interrelated factors, namely tumor/neck ultrasound characteristics, patient characteristics, and characteristics of the health-care teams. According to the analysis of these key factors in each of these fields, patients suitable for AS can be screened out accurately. However, the effectiveness of this evaluation method still needs to be verified. In summary, as there is currently no unified standard, we need to consider multiple aspects. Some points are also meaningful when screening patients. First, PTMC with high-risk features, including clinical LNMs, distant metastases, and invasion of adjacent organs, should not be treated with AS and should be operated on immediately and treated with radioiodine postoperatively if needed. Second, AS should be performed only when there are no malignant cytological findings, such as high cell variants, which suggest strong invasiveness of PTC. For small nodules with malignant characteristics, careful selection is necessary. Third, appropriate multidisciplinary teams are needed to accurately assess the appropriate population for AS to fully reach joint decisions with patients and to adhere to regular follow-up. To date, several clinicopathological features were reported to be related to the prognosis of patients with PTMC, such as age, pregnancy, and gene mutations, which might also significantly influence the choice of initial treatment. Common gene mutations in PTC, such as *BRAF*, *NRAS*, telomerase reverse transcriptase (*TERT*), etc., may have predictive significance for the prognosis of PTC, but their value in the diagnosis of low-risk PTMC has not been proven, which needs further confirmation. Besides, tumor multiplicity and family history may not be considered to be associated with PTMC progression; Thus, these individuals are also currently candidates for AS. Concerning the degree of calcification, and vascularity, in combination with other thyroid diseases, it is not clear how they are related to the progression of PTMC, and further evidence is warranted.

In addition to unclear identification of low-risk PTMC, doctors and patients are also important in affecting the implementation of AS. Physicians' recommendations have a significant effect on the choice of treatment for patients with low-risk PTMC. Despite widespread recognition of the benefits of AS among physicians treating low-risk PTMC, most physicians are reluctant to offer it because of the lack of reliable evidence, guidelines, and specific implementation protocols. Some doctors even do not understand or recognize AS; So, they should have a comprehensive understanding of the AS strategy to judge whether patients are suitable for AS and know how to implement AS for patients. Another severe concern is that, if a patient's condition deteriorates or the patient even dies, the doctor who recommends AS could be blamed, which causes many doctors to be reluctant to offer AS, although their patients might be suitable for it. The relevant policies specifically for AS must be improved, the consent of patients should be fully solicited, and informed consent forms should be signed. Subsequent monitoring should also be guided and conducted by a professional team.

According to the above suggestions, it might be possible to avoid the occurrence of medical accidents.

The choice of AS is ultimately up to the patients after low-risk PTMC patients have discussed it with their doctors. Therefore, it is important to understand the factors that influence the patient's choice. Generally, patients' ages, tumor sizes, and the use of decision aids were associated with the initial treatment choice for low-risk PTMC. Evidence indicates that doctors, family members, and the media are the main factors influencing patients' choices. Family members usually hope that patients can be free of cancer and choose surgery immediately while the information from the media often guides patients in choosing AS. Another important issue that patients are concerned about is the QoL after receiving different treatments. Traditional PTMC treatment is still surgical, including total thyroidectomy and unilateral lobectomy. Studies verified that patients who underwent unilateral lobectomy had a better QoL than those who underwent total thyroidectomy. It is also important to consider the psychological concerns related to cancer in the context of the patient's life. Some studies indicated that the concerns of TC survivors were related to age, family situation, time, and other factors, which must be further confirmed, as well as developing effective psychological support strategies for them. A Japanese study compared the QoL of patients with low-risk PTMC who chose AS and surgery and found that anxiety scores were higher in the AS group than in the surgery group, but the authors mentioned that anxiety could come from how doctors explained AS to patients and clinical management strategies and the level of concern reported by patients undergoing AS decreased over time. Thus, concerns about cancer should not be considered a factor against implementing AS in patients with low-risk PTMC, and high-quality studies are still warranted to compare psychological status and QoL between undergoing surgery and choosing AS.

Another issue that cannot be ignored is that the excessive diagnosis and treatment of low-risk PTMC has brought huge clinical and economic burdens to societies in various countries. There have been several studies comparing the cost difference between surgery and AS. A study in Japan reported that the 10-year total cost of immediate surgery was 4.1 times higher than that of AS in Kuma Hospital. A study in Hong Kong, China, made the same point that AS not only resulted in cost savings during the first 16 years but also remained cost-effective thereafter, independent of patient age, complication rate, or PTMC progression. Overall, the cost-effectiveness of PTMC treatment depends on AS-related health status and life expectancy after diagnosis, and it could be influenced by each country's national health insurance coverage and the interval of thyroid ultrasound during follow-up.

In summary, AS is one of the important choices for low-risk PTC, which requires the understanding and cooperation of both doctors and patients. But more significantly, more efforts need to be made to promote standardized diagnosis and treatment and to differentiate low-risk PTMC, which is the foundation of AS. With the deepening of research, more evidence from all over the world will be obtained,

the corresponding guidelines will become more detailed, the concerns of doctors and patients will be reduced, and AS will be better used.

Funding

This work was supported by grants from the Research Fund for Public Welfare, National Health and Family Planning Commission of China (No. 201402005) and the Clinical Research Fund of Chinese Medical Association (No. 15010010589).

Conflicts of interest

None.

References

1. Haugen BR, Alexander EK, Bible KC, Doherty GM, Mandel SJ, Nikiforov YE, *et al.* 2015 American Thyroid Association Management Guidelines for adult patients with thyroid nodules and

- differentiated thyroid cancer: The American Thyroid Association Guidelines Task Force on thyroid nodules and differentiated thyroid cancer. *Thyroid* 2016;26:1–133. doi: 10.1089/thy.2015.0020.
2. Xia CF, Dong XS, Li H, Cao MM, Sun DQ, He SY, *et al.* Cancer statistics in China and United States, 2022: profiles, trends, and determinants. *Chin Med J* 2022;135:584–590. doi: 10.1097/CM9.0000000000002108.
3. Ito Y, Uruno T, Nakano K, Takamura Y, Miya A, Kobayashi K, *et al.* An observation trial without surgical treatment in patients with papillary. *Thyroid* 2003;13:381–387. doi: 10.1089/105072503321669875.
4. Molinaro E, Campopiano MC, Pieruzzi L, Matrone A, Agate L, Bottici V, *et al.* Active surveillance in papillary thyroid microcarcinomas is feasible and safe: Experience at a single Italian center. *J Clin Endocrinol Metab* 2020;105:e172–e180. doi: 10.1210/clinem/dgz113.
5. Brito JP, Ito Y, Miyauchi A, Tuttle RM. A clinical framework to facilitate risk stratification when considering an active surveillance alternative to immediate biopsy and surgery in papillary microcarcinoma. *Thyroid* 2016;26:144–149. doi: 10.1089/thy.2015.0178.

How to cite this article: Zhang XQ, Aihaiti R, Teng WP, Shi XG. Factors affects the implementation of active surveillance therapy for low-risk papillary thyroid microcarcinoma. *Chin Med J* 2024;137:1888–1890. doi: 10.1097/CM9.0000000000003083